# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



| Applicant's or agent's file reference<br>4239-66168-02 | **FOR FURTHER ACTION** See Form PCT/IPEA/416 | |
|---|---|---|
| International application No.<br>PCT/US2004/019489 | International filing date *(day/month/year)*<br>18.06.2004 | Priority date *(day/month/year)*<br>19.06.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>C12Q1/68 | | |
| Applicant<br>THE GOVERNMENT OF THE UNITED STATES OF AMERICA ... | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 20.06.2005 | 02.12.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office - P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040 Tx: 31 651 epo nl<br>Fax: +31 70 340 - 3016 | Authorized Officer<br>Cornelis, K<br>Telephone No. +31 70 340-8957 |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/US2004/019489

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-105 as originally filed

**Sequence listings part of the description, Pages**

1-445 as originally filed

**Claims, Numbers**

1-49 as originally filed

**Drawings, Sheets**

1/8-8/8 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/019489

## Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 4,5,8,9,15 (completely) and 1-3,6,7,10-14,16-49 (partially) .

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 2-5, 8-16,19-42, 44-49 |
| | No: | Claims | 1,6,7,17,18,43 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-49 |
| Industrial applicability (IA) | Yes: | Claims | 1-49 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

   **see separate sheet**

**Supplemental Box relating to Sequence Listing**

**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Reference is made to the following documents:

D1: UEDA T ET AL: "Identification of coding single-nucleotide polymorphisms in human taste receptor genes involving bitter tasting." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 6 JUL 2001, vol. 285, no. 1, 6 July 2001 (2001-07-06), pages 147-151, XP002301613 ISSN: 0006-291X

D2: KIM UN-KYUNG ET AL: "Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide." SCIENCE. 21 FEB 2003, vol. 299, no. 5610, 21 February 2003 (2003-02-21), pages 1221-1225, XP002301614 ISSN: 1095-9203

D3: SHI PENG ET AL: "Adaptive diversification of bitter taste receptor genes in Mammalian evolution." MOLECULAR BIOLOGY AND EVOLUTION. MAY 2003, vol. 20, no. 5, May 2003 (2003-05), pages 805-814, ISSN: 0737-4038

D4: WO 01/18050 A (HOON MARK ; MUELLER KEN (US); RYBA NICK (US); US HEALTH (US); UNIV CAL) 15 March 2001 (2001-03-15)

D15: BERND BUFE: "Dissertation zur Erlangung des Doktorgrades an der Universität Potsdam: Identifizierung und Charakterisierung von Bitterezeptoren" [Online] May 2003 (2003-05), , POTSDAM , XP002318541 Retrieved from the Internet: URL:http://pub.ub.uni-potsdam.de/2004/0013 /bufe.pdf> [retrieved on 2005-02-17]

D16: LIPSHUTZ ET AL "High density synthetic oligonucleotide arrays", January 1999, Nature Genetics Supplement, Volume 21, page 20-24, XP002182912

D17: DATABASE EMBL [Online] 29 April 2002 (2002-04-29), "Homo sapiens candidate taste receptor TAS2R44 gene, complete cds." XP002318542 retrieved from EBI accession no. EM_PRO:AF494228 Database accession no. AF494228 SEQ

D18: WO 01/77676 A (SENOMYX INC) 18 October 2001 (2001-10-18)

## IV. Lack of UNITY of invention

The problem underlying the present application appears to be the identification of genetic variations in bitter taste receptors (T2R). The single general concept which may possibly link the subject matter of claims 1-49 seems to be the provision of T2R variant specific nucleic acid molecules which comprise at least 1 SNP.

D3 discloses the T2R genes used in the current application with their accession number. D1 reports of 6 SNPs in the cDNA of T2R3, T2R4, T2R5. D2 discloses 3 SNPs and 5 haplotypes for the PTC gene, which corresponds to the T2R38 gene according to the application. The identified haplotypes are linked with the ability to taste PTC.

Therefore, the general concept of the application is not novel. The single general concept of the application is therefore not a single inventive concept, the application hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.
The problem to be solved by the the claimed subject matter can be formulated as providing additional variants in several T2R genes. Each of the SNPs disclosed in Figure 1 and the haplotypes of Table 7a and c (Claims 1 and 6) represent a solution. No special technical feature (in the sense of Rule 13.2 PCT) links all these disclosed molecules. Hence the different sequences lack unity according to Rule 13.1 PCT.
The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT.
In the light of the already disclosed prior art, the Search Authority considers the main contribution of the application to reside in the provision the collection of the haplotypes as defined in Table 7. Therefore this was considered as the "main invention", even though this is not referred to in claim 1 (Guidelines 10.61).
This Authority considers that there are 23 inventions covered by the claims indicated as follows:

**Invention 1**: Claims 8, 9, 15 (completely) and 6,7, 10-14,16,18-33,37,38,45-49 (partially) directed to a collection of T2R variant nucleic acids, comprising at least 2 T2R1 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R1 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 2:** Claims 4-5, 8, 9, 15 (completely) and 1-3, 6, 7, 10-14, 16-49 (partially): directed to a T2R3 variant specific nucleic acid molecule comprising at least one SNP, a collection of T2R variant nucleic acids, comprising at least 2 T2R3 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R3 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 3** Claims 8, 9, 15 (completely) and 6,7, 10-14,16,18-33,37,38,45-49 (partially) directed to a collection of T2R variant nucleic acids, comprising at least 2 T2R4 variant

specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R4 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 4:** Claims 4-5, 8, 9, 15 (completely) and 1-3, 6, 7, 10-14, 16-49 (partially): directed to a T2R5 variant specific nucleic acid molecule comprising at least one SNP, to a collection of T2R variant nucleic acids, comprising at least 2 T2R5 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R5 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 5:** Claims 8, 9, 15 (completely) and 6,7, 10-14,16,18-33,37,38,45-49 (partially) directed to a collection of T2R variant nucleic acids, comprising at least 2 T2R7 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R7 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 6-8:** Claims 4-5, 8, 9, 15 (completely) and 1-3, 6, 7, 10-14, 16-49 (partially): directed to respectively a T2R8, 9,10 variant specific nucleic acid molecule comprising at least one SNP, respectively, to a collection of T2R variant nucleic acids, comprising at least 2 T2R8,9,10 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R8,9,10 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste..

**Invention 9:** Claims 8, 9, 15 (completely) and 6,7, 10-14,16,18-33,37,38,45-49 (partially) directed to a collection of T2R variant nucleic acids, comprising at least 2 T2R13 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R13 isoform

specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 10-15:** Claims 4-5, (completely) and 1-3,17, 18, 34-36, 39-44, 47-49 (partially): directed to respectively a T2R14-41 variant specific nucleic acid molecule comprising at least one SNP, respectively, to a collection of T2R variant nucleic acids, comprising at least 2 T2R14-41 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R14-41 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 16:** Claims 4-5, (completely) and 1-3,17, 18, 34-36, 39-44, 47-49 (partially): directed to respectively a T2R43 variant specific nucleic acid molecule comprising at least one SNP, an array comprising at least 2 such molecules, an isolated polypeptide fragment comprising an amino acid change as in Figure 1, and a method to screen for compounds useful for modulating bitter taste.

**Invention 17-21:** Claims 4-5, (completely) and 1-3,17, 18, 34-36, 39-44, 47-49 (partially): directed to respectively a T2R44-49 variant specific nucleic acid molecule comprising at least one SNP, respectively, to a collection of T2R variant nucleic acids, comprising at least 2 T2R44-49 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R44-49 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 22:** Claims 8, 9, 15 (completely) and 6,7, 10-14,16,18-33,37,38,45-49 (partially) directed to a collection of T2R variant nucleic acids, comprising at least 2 T2R50 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R50 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**Invention 23:** Claims 4-5, 8, 9, 15 (completely) and 1-3, 6, 7, 10-14, 16-49 (partially): directed

to a T2R60 variant specific nucleic acid molecule comprising at least one SNP, to a collection of T2R variant nucleic acids, comprising at least 2 T2R4 variant specific nucleic acid molecules which comprise at least one SNP listed in Table 7, an array comprising said collection, an isolated polypeptide fragment comprising an amino acid change as in Figure 1 or Table 7, an isolated nucleic acid molecule, a kit comprising a T2R4 isoform specific antibody, and a method to screen for compounds useful for modulating bitter taste.

**V. Reasoned statement with regards to novelty and inventive step**

**INVENTION 17**

**1 NOVELTY**

1.1 D17 discloses an isolated T2R44 variant specific nucleic acid molecule comprising 930 contiguous nucleotides spanning all the SNPs of T2R44 identified as "new" in Figure 1, thus disclosing the subject matter of claim **1**.

1.2 D15 also refers to the accession number of D17, thereby disclosing the subject matter of claim 1. D15 further discloses a collection of 8 isolated T2R44 variant specific nucleic acid molecules each comprising at least about 10 contiguous nucleotides spanning at least 1 T2R44 SNP position listed in Table 7 (page 61-62, together with the description of the SNP analysis on pages 18-19). D15 discloses oligonucleotides which are specific for a T2R43 comprising at least 1 SNP referred to as new in Figure 1 (Tabelle 2.1). Claim 43 differs from D15 in that the kit additionally comprisises instructions. Instructions are considered to be merely a presentation of information, which is not considered a technical feature. Hence, the subject matter of claim 43 does not differ from D15 by any technical feature, the claim can therefore not be considered new. D15 hence discloses the subject matter of claims **1, 6, 7,43.**

1.3 D18 discloses an isolated T2R44 variant specific nucleic acid molecule comprising 928 contiguous nucleotides spanning all the SNPs of T2R44 identified as "new" in Figure 1 (page 73, T2R64 sequence SEQ ID NO 11). It also discloses an isolated T2R isoform polypeptide fragment which comprises 310 amino acids of SEQ ID NO 34 (Claim 87, SEQ ID NO 12). D18 therefore discloses the subject matter of claims **1, 17, 18.**

1.4 Claims **1,6,7,17,18,43** are not new (Article 33(2) PCT).

**2 INVENTIVE STEP**

2.1 Claim 23 refers to isolated nucleic acids comprising a sequence as in SEQ ID Nos 187,189,191,197,199. These sequences differ from each other and the wild type sequence of T2R44 in that different nucleotides are present at one or more of the sites 103, 484,599, 656,680,827,843. D15 is considered the most relevant prior art for the subject matter of claim 23 and discloses isolated nucleic acid molecules with a sequence as the wild type T2R44 and variants with several SNPs.
Claim **23 differs** from D15 in that the SNPs occur at different positions. The technical effect of this difference is that molecules which represent different haplotypes of T2R44 are available. The problem solved by the subject matter of claim 23 can therefore be seen as the provision of alternative haplotypes of T2R44.
The solution of the application with respect to invention 17 is the provision of nucleic acid molecules with a sequence as in SEQ ID 187,189,191,197,199.
These solutions cannot be considered as inventive in view of D15, which already discloses that there are several SNPs and therefore haplotypes of T2R44. The person skilled in the art who wanted to solve the above stated problem would use a procedure as described in D15 (i.e. sequencing of PCR amplified fragments of receptors) to find more SNPs/haplotypes of this gene. The sequences of claim 23 are some sequences of those which the person skilled in the art would find when performing experiments as in D15 (page 19). There seems to be no effect associated with these particular haplotypes of T2R44, therefore they are just some of many possible molecules which would solve the same problem. The provision of a new "actual" variation from an "actual" individual or population does not have any technical effect, a new variant without an associated effect (e.g. sensitivity to some compounds) is not considered inventive.
**Claim 23 and dependent claims 24 and 25** are therefore not considered inventive (Article 33(3) PCT).

2.2 D18 discloses a method of screening compounds useful for modulating bitter taste, comprising: contacting a test compound with a host cell or membrane thereof that expresses a T2R taste receptor, e.g. the one corresponding to SEQ ID NO 11 (claim 108) and detecting a change in the expression (claim 114, page 62 line 30) or activity of the T2R taste receptor, or detecting binding of a compound to the T2R taste receptor or detecting a change in intracellular or extracellular cAMP, cGMP, IP3 or Ca2+ (page 60, lines 19-27). The gene product may be fused to a sequence that facilitates localisation to the cell membrane, wherein that sequence is the N-terminal sequence of

the rhodopsin protein (page 59 lines 6-11). The cell can be an eukaryotic cell, such as HEK-293 cells (page 62, line 6). The change in intracellular $Ca^{2+}$is detected by measuring a change in fluorescence in the cell (page 62, line 12).
The **difference** between **claim 26** and D18 is thus the use of other T2R44 haplotypes, namely the haplotypes with a sequence as in SEQ ID NO 187,189,191,197,199, encoding a polypeptide as in SEQ ID NO 188,190,192,198,200. The technical effect of this difference is that effect of compounds on another haplotype of T2R44 can be evaluated. Thus the problem solved by claim 26 is the provision of alternative haplotypes of T2R44 to be used in a screening method for bitter taste modulators.
The use of the particular haplotypes of claim 26 does not have any effect, the fact that new or different haplotypes are used does not render the method inventive. For similar reasons as outlined for claim 23, the provision of these haplotypes cannot be considered inventive (Article 33(3) PCT).

2.3 Further dependent and independent claims are also considered to be not inventive as they are variants of products or methods already disclosed in D1-D4, D15-D18 and do not appear to have any further technical effect associated with using these methods or products with a further SNP or haplotype of T2R44. Claims 1-49 are therefore considered not inventive (Article 33(3) PCT).

2.4 The application states that the inventive aspect resides in the provision of a comprehensive set of haplotypes of all T2R receptors. However, as this is not currently reflected in the claims, the validity of such statements has not been considered.